Steroidal Pyrazolines

Panayotis Catsoulacos (1) and C. I. Stassinopoulou

Department of Chemistry, Nuclear Research Center "Demokritos",
Aghia Paraskevi Attikis, Athens, Greece

Received September 7, 1977

Reaction of 21-benzal-5-pregnen-3β-ol-20-one acetate with phenylhydrazine or *p*-methoxyphenylhydrazine in the presence of hydrochloric acid yielded 3β-acetoxy-1′,5′-diphenyl-5-pregneno[20,21-c]pyrazoline. Alkaline hydrolysis of the 3β-acetoxy group followed by Oppenauer oxidation furnished the 3-oxo-1′,5′-diphenyl-4-pregneno[20,21-c]pyrazoline. The ir, nmr and mass spectra are described.

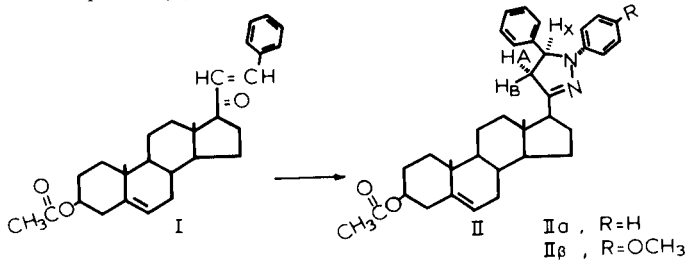
J. Heterocyclic Chem., **15**, 313 (1978)

A variety of conditions and reagents have been used for cyclizing α,β-unsaturated carbonyl compounds with phenylhydrazine to give pyrazolines, through phenylhydrazone formation (2).

In the course of our work on heterocyclic steroids for biological purposes (3-8), we have attempted to react phenylhydrazine with 21-benzal-5-pregnen-3β-ol-20-one acetate.

When compound I was heated under reflux with phenylhydrazine for 48 hours, pyrazoline IIa and starting material were obtained.

The condensation of phenylhydrazine or *p*-methoxyphenylhydrazine with 21-benzal-5-pregnen-3β-ol-20-one acetate (9) in the presence of hydrochloric acid gave the corresponding pyrazolines IIa and IIb in good yield.



Our attempts to isolate the intermediate phenylhydrazone by exposing I to phenylhydrazine with 21-benzal-5-pregnen-3β-ol-20-one acetate in ethanol at room temperature resulted in the isolation of the starting material.

As the phenyl ring of the benzylidene compound I is *trans* to the carbonyl then the ring closure of the intermediate phenylhydrazone accomplished by the *trans* addition to the double bond, forming pyrazoline II (10).

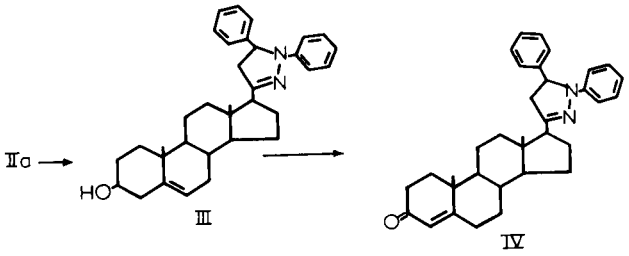
The structure of the pyrazolines IIa and IIb was deduced from their pmr spectrum (shown in Table I). The two non-equivalent protons on C-4′ and the proton on C-5′ of the pyrazoline ring in compounds IIa and IIb give ABX patterns. The assignments were checked by double resonance experiments. By irradiating 5′-HX protons 4′-HB gave a simple AB spectrum. In turn, when first 4′-HA and then 4′-HB were irradiated a doublet was obtained each time for 5′-HX. The J_{BX} viccinal coupling constant is larger than the J_{AB} indicating that 5′-HX is *trans* to 4′-HB and *cis* to 4′-HA.

Table I

Nmr Data (Deuteriochloroform) for Pyrazolines IIa and IIb

Protons	IIa Chemical Shifts (ppm)	IIb
5′-Phenyl	2.66	2.64
1′-Phenyl	2.79-3.37	3.18
6-H	4.58	4.59
5′-HX	5.00	5.14
3-H	5.35	5.35
5′-*p*-Methoxy	--	6.26
4′-HB	6.62	6.67
4′-HA	7.22	7.22
3β-Acetate	7.92	7.92
19-Methyl	8.94	8.94
18-Methyl	9.25	9.25
	Coupling constants	cps
J_{AB}	17.5	17
J_{AX}	8	9.5
J_{BX}	12	11.5

The molecular weights of IIa and IIb were 536 and 566 respectively (mass spectrometry). A peak at m/e 459 (IIa) and m/e 489 (IIb) with the metastable ions at m/e 393.1 and 422.5 explains that these peaks (m/e 459 and 489) correspond to the loss of phenyl radical from the molecular ions as established by Aubagnac and co-workers (11). Compounds IIa and IIb gave a positive Knorr (12) and bromine (13) test for a pyrazoline; their infrared spectra showed absence of NH absorption and a characteristic peak at 1600 cm^{-1} for the heterocyclic ring. Basic hydrolysis of the pyrazoline acetate IIa following Oppenauer oxidation gave 3-oxo-4pregneno[20,21-c]-1′,5′-diphenylpyrazoline (IV).



The structure of IV was confirmed by its analytical and spectral data, 1665 (CO), 1610 (C=C), 1600 cm^{-1} (C=N). The singlet for the vinyl proton in the nmr spectrum of IV appears at τ 5.73. Molecule weight was 492.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. Nmr spectra were determined with a Varian XL-100 instrument, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Mass spectra were obtained at 70 eV by direct insertion into the ion source of a Hitachi Perkin-Elmer RMU-6M instrument.

3β-Acetoxy-5-pregneno[20,21-*c*]-1′,5′-diphenylpyrazoline (IIa).

To a solution of 1 mmole of I (9) in 30 ml. of ethanol containing three drops of concentrated hydrochloric acid, 3 mmoles of phenylhydrazine was added and the mixture was refluxed for 21 hours. Part of the solvent was evaporated and the precipitate was collected by filtration, washed well with cold ethanol, and air-dried, yielded 58% after recrystallization from chloroform-methanol, m.p. 187-188°; ir: ν max 1730, 1235 (CO), 1595 (C=N), 740, 690, 685 cm^{-1} (aromatic rings).

Anal. Calcd. for $C_{36}H_{44}N_2O_2$: C, 80.60; H, 8.17; N, 5.22. Found: C, 80.17; H, 8.24; N, 5.32.

When compound I (1 mmole) was treated with phenylhydrazine (1.5 mmoles) in 50 ml. of ethanol under reflux for 30 or 60 hours, a mixture of starting material and pyrazoline was isolated.

Attempted Reaction of Benzylidene I with Phenylhydrazine at Room Temperature.

Compound I (1 mmole) was dissolved in 400 ml. of absolute ethanol and to the solution was added 2 mmoles of phenylhydrazine. The mixture was agitated at room temperature for 120 hours. Water was added and the precipitate was collected by filtration to give 440 mg. unchanged benzylidene I.

3β-Acetoxy-5-pregneno[20,21-*c*]-1′-(*p*-methoxyphenyl)-5′-phenylpyrazoline (IIb).

To a solution of I (1 mmole) in 10 ml. of pyridine, 1.1 mmoles of *p*-methoxyphenylhydrazine hydrochloride was added and the mixture was heated under reflux for 48 hours. The solvent was evaporated under reduced pressure and water was added to the residue. The precipitate removed by filtration, washed with water and air-dried, produced pyrazoline IIb in 63% yield, m.p. 238-239° (chloroform-methanol); ir: ν max 1725, 1235 (CO), 1600 (C=N), 815, 755 and 690 (aromatic rings).

Anal. Calcd. for $C_{37}H_{46}N_2O_3$: C, 78.44; H, 8.12; N, 4.94. Found: C, 78.15; H, 7.99; N, 4.89.

3β-Hydroxy-5-pregneno[20,21-*c*]-1′,5′-diphenylpyrazoline (III).

Pyrazoline IIa (0.536 g.) was dissolved in 30 ml. of methanol containing 0.4 g. of sodium hydroxide. The mixture was agitated for 2 hours at room temperature. The reaction mixture was poured into water and the precipitate collected by filtration, washed several times with water, and dried to yield III, 0.430 g. (87%), m.p. 203-204° (chloroform-methanol); ir: ν max 3360 (OH), 1590 (C=N), 740, 690, 685 cm^{-1} (aromatic rings).

Anal. Calcd. for $C_{34}H_{42}N_2O$: C, 82.60; H, 8.50; N, 5.66. Found: C, 82.54; H, 8.78; N, 5.62.

3-Oxo-4-pregneno[20,21-*c*]-1′,5′-diphenylpyrazoline (IV).

A solution of 0.4 g. of 3-hydroxy-5-pregneno[21,21-*c*]-1′,5′-diphenylpyrazoline in 5 ml. of cyclohexanone, 20 ml. of dry dioxane and 16 ml. of dry toluene was distilled slowly as a solution of 0.450 g. of aluminium isopropylate in 3 ml. of dry toluene was added. Distillation was continued for two hours as 10 ml. of toluene was added and 25 ml. of distillate was collected. Then the mixture was refluxed for four hours and left to stand at room temperature overnight. The mixture was filtered to remove the precipitate containing the aluminum. The filtrate was distilled, extracted with chloroform and evaporated. The residue was chromatographed on a column of silica gel (15 g.) prepared with chloroform. Elution with chloroform gave pyrazoline IV, m.p. 243-245° (chloroform-methanol); ir: ν max 1665 (CO), 1610 (C=C) and 1590 cm^{-1} (C=N).

Anal. Calcd. for $C_{34}H_{40}N_2O$: C, 82.92; H, 8.13; N, 5.70. Found: C, 82.60; H, 8.70; N, 5.54.

REFERENCES AND NOTES

(1) To whom correspondence should be addressed.

(2) R. C. Elderfield, "Heterocyclic Compounds", Vol. 5, J. Wiley and Sons, Inc., New York, N. Y., 1957, pp. 48-89.

(3) P. Catsoulacos, *J. Heterocyclic Chem.*, **10**, 93 (1973).

(4) P. Catsoulacos and E. Souli, *ibid.*, **11**, 87 (1974).

(5) P. Catsoulacos and E. Souli, *ibid.*, **12**, 193 (1975).

(6) P. Catsoulacos and N. Kyriakidis, *ibid.*, **12**, 1313 (1975).

(7) P. Catsoulacos and E. Souli, *Bull. Soc. Chim. France*, 2313 (1975).

(8) P. Catsoulacos and B. Papadopoulos, *J. Heterocyclic Chem.*, **13**, 159 (1976).

(9) R. E. Marker, E. L. Wittle, E. M. Jones and H. M. Crooks, *J. Am. Chem. Soc.*, **64**, 1282 (1942).

(10) A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 298 (1962).

(11) J. L. Aubagnac, R. Jacquier and M. Ramos, *Bull. Soc. Chim. France*, 737 (1974).

(12) L. Knorr, *Ber.*, **26**, 100 (1893).

(13) L. C. Raiford and W. J. Peterson, *J. Org. Chem.*, **1**, 544 (1937).